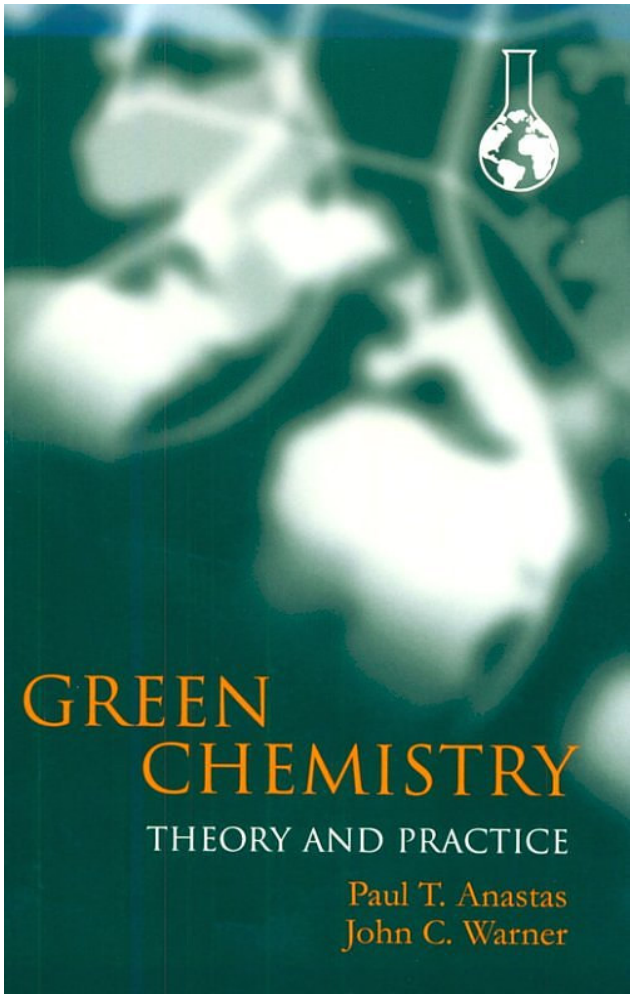
Green Chemistry and Engineering Concepts Applied to Large Molecule Biopharmaceutical Drugs- Preliminary Thoughts

Berkeley W. Cue, Jr., Ph.D.
ctcuefamily@aol.com
MA OTC Conference
Boxborough, MA
April 5, 2007

Outline

- What are green chemistry and green engineering?
- The ACS Green Chemistry Institute Pharmaceutical Roundtable
- What are the biotechnology opportunities for small molecule manufacture?
- What is the “lay of the land” for green chemistry and engineering opportunities for large molecule (vaccine, protein, MAb)?
- Some next steps and summary

What is Green Chemistry?



"…the utilization of a set of principles that reduces or eliminates the use or generation of hazardous substances in the design, manufacture and application of chemical products."

*Source: Paul T. Anastas and John C. Warner, *Green Chemistry: Theory and Practice* (New York, NY: Oxford University Press Inc., 1998).
ISBN 0 19 850698 8

12 Principles of Green Chemistry

1. Prevention
2. Atom Economy
3. Less Hazardous Chemical Synthesis
4. Design Safer Chemicals
5. Safety Solvents & Auxiliaries
6. Design for Energy Efficiency
7. Use Renewable Feedstocks
8. Reduce Derivatives
9. Catalysis
10. Design for Degradation
11. Real-Time Analysis for Pollution Prevention
12. Inherently Safer Chemistry for Accident Prevention

What is Green Engineering?

Green engineering is the design, commercialization, and use of processes and products, which are feasible and economical while minimizing

1)generation of pollution at the source and

2) risk to human health and the environment.

The discipline embraces the concept that decisions to protect human health and the environment can have the greatest impact and cost effectiveness when applied early to the design and development phase of a process or product

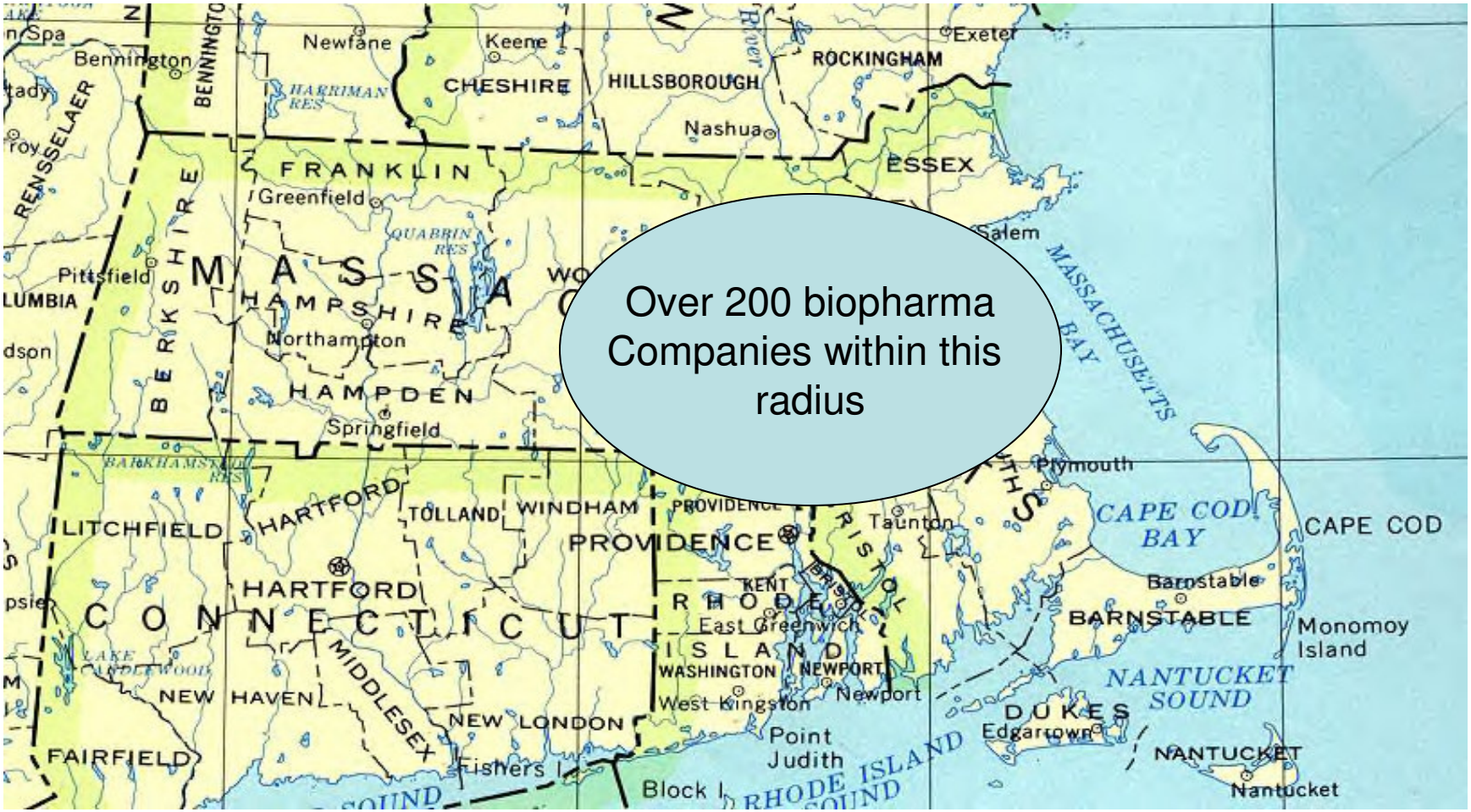
12 Principles of Green Engineering

Anastas and Zimmerman, Environmental Science and Technology, March 2003, p. 96

1. Designers need to strive to ensure all materials and energy inputs and outputs are as inherently non hazardous as possible
2. It is better to prevent waste than to treat or clean up waste after it is formed
3. Separation and purification operations should be designed to minimize energy consumption and materials use
4. Products, processes, and systems should be designed to maximize mass, energy, space, and time efficiency
5. Products, processes, and systems should be “output pulled” rather than “input pushed” through the use of energy and materials.
6. Embedded entropy and complexity must be viewed as an investment when making design choice on recycle, reuse or beneficial disposition
7. Targeted durability, not immortality, should be a design goal
8. Design for all unnecessary capacity or capability (e.g., “one size fits all”) solutions should be considered a design flaw
9. Material diversity in multi component products should be minimized to promote disassembly and value retention
10. Design of products, processes, and systems must include integration and interconnectivity with available energy and material flows
11. Products, processes and systems should be designed for performance in a commercial “afterlife”
12. Material and energy inputs should be renewable rather than depleting

Massachusetts Biopharmaceutical Companies

www.massmeansbusiness.com



Map source:http://www.lib.utexas.edu/maps/united_states/massachusetts

Green Chemistry Performance Metrics: E-Factor
Roger Sheldon, *Chem Tech*, 1994, **24**, 38

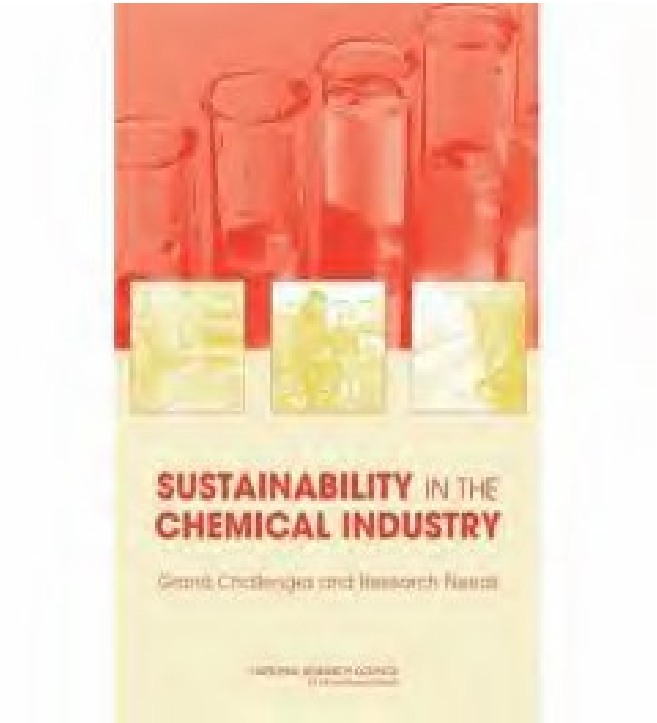
Table 1. Sectors of the chemical industry by quantity of byproduct per kg of product

Industry Sector	***Product tonnage***	***kg byproducts/ kg of product***
Oil refining	**10^6 - 10^8**	**ca 0.1**
Bulk Chemicals	**10^4 – 10^6**	**<15**
Fine Chemicals	**10^2 – 10^4**	**5-50**
Pharmaceuticals	**10^1 – 10^3**	**25-100+**

More than 80% of pharmaceutical manufacturing waste is solvent

See: Gonzalez, Curzons, Constable and Cunningham, Int. J. LCA, **9** (2), 114 (2004); Constable, Gonzalez and Henderson, Org. Process R and D, **11**, 133(2007); R. DiCola, Pharmaceutical Environmental Group Conference, Philadelphia, 2004

Sustainability in the Chemical Industry: Grand Challenges and Research Needs - A Workshop Report (2005) by The National Research Council



The 8 Grand Challenges

- Green and sustainable chemistry and engineering
- Life cycle analysis
- Toxicology
- Renewable chemical feedstocks
- Renewable fuels
- Energy intensity of chemical processing
- Separation, sequestering and utilization of carbon dioxide
- Sustainability education

Pharmaceutical Roundtable (GCIPR)

- A coalition between the ACS Green Chemistry Institute (GCI) and pharmaceutical corporations united by a shared commitment to integrate the principles of green chemistry and engineering into the business of drug discovery and production.
- **Mission:** To catalyze the implementation of green chemistry and engineering in the pharmaceutical industry globally.
- **Strategic Priorities**
  - Informing & Influencing the Research Agenda
  - Tools for Innovation
  - Education Resource
  - Global Collaboration

AstraZeneca

Lilly

MERCK

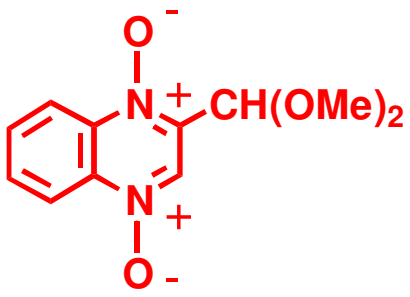
Pfizer

gsk GlaxoSmithKline

Johnson & Johnson

Schering-Plough

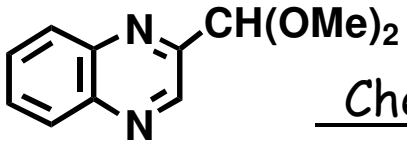
Chemical & Biocatalytic Routes to QCA



di-*N*-oxide

$Na_2S_2O_4/H_2O$

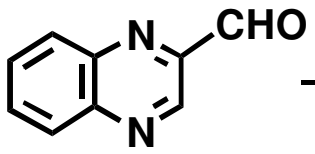
EtOH



Chemical Route

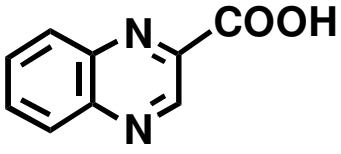
- 3 steps, 35% yield
- Di-*N*-oxide: mutagenic & high energy intermediate

aq. HCl



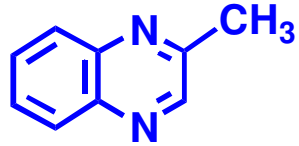
35% H_2O_2

10% NaOH



QCA

Pseudomonas putida whole cells



2-Methylquinoxaline

Biocatalytic Route

- 1 step (3 enzyme reactions), 86% yield
- Aqueous reaction at 28°C

Chemical & Biocatalytic Process Comparison

Raw materials for 1 kg QCA

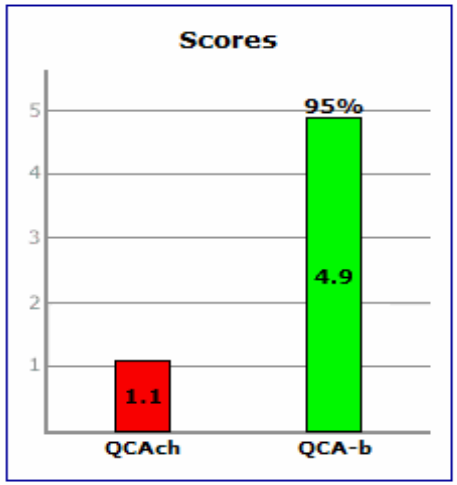
Chemical Process			*P. putida* Process	
di-*N*-oxide	3.9 kg		2-methylquinoxaline	0.97 kg
$Na_2S_2O_4$	5.7 kg		benzyl alcohol	2.9 L
35% H_2O_2	6.5 L		*p*-xylene	0.9 L
4N HCl	13.6 L		4N HCl	3.8 L
10% NaOH	11.7 L		10% NaOH	1.7 L
chloroform	142 L		inorganic salts	0.75 kg
N,*N*-dimethylacetamide	36 L		trace elements	0.005 kg
ethanol	18 L		H_2O	79 L

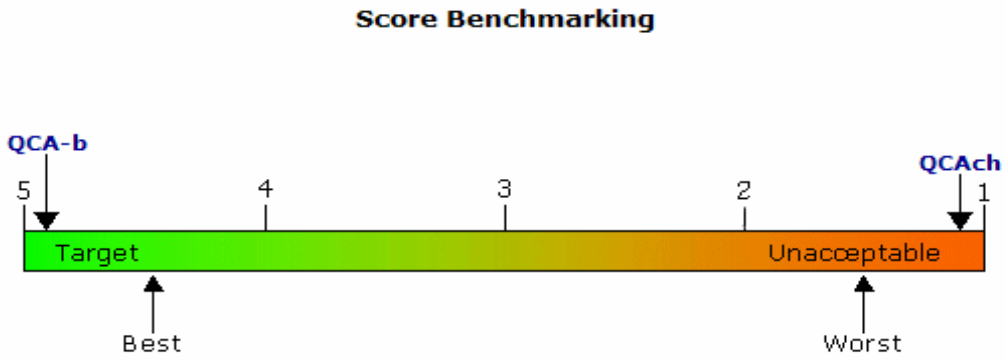
- Biocatalytic route avoids hazardous di-*N*-oxide and uses 4x less starting material
- Reduced organic solvent consumption for biocatalytic route (3.8 L/kg QCA) vs. chemical process (196 L/kg QCA)
- John Wong, et. al., OPRD, **2002**, 6, 477-481.

GSK Life Cycle Assessment Tool

Fast Lifecycle Assessment for Synthetic Chemistry (FLASC)

Route Assessment



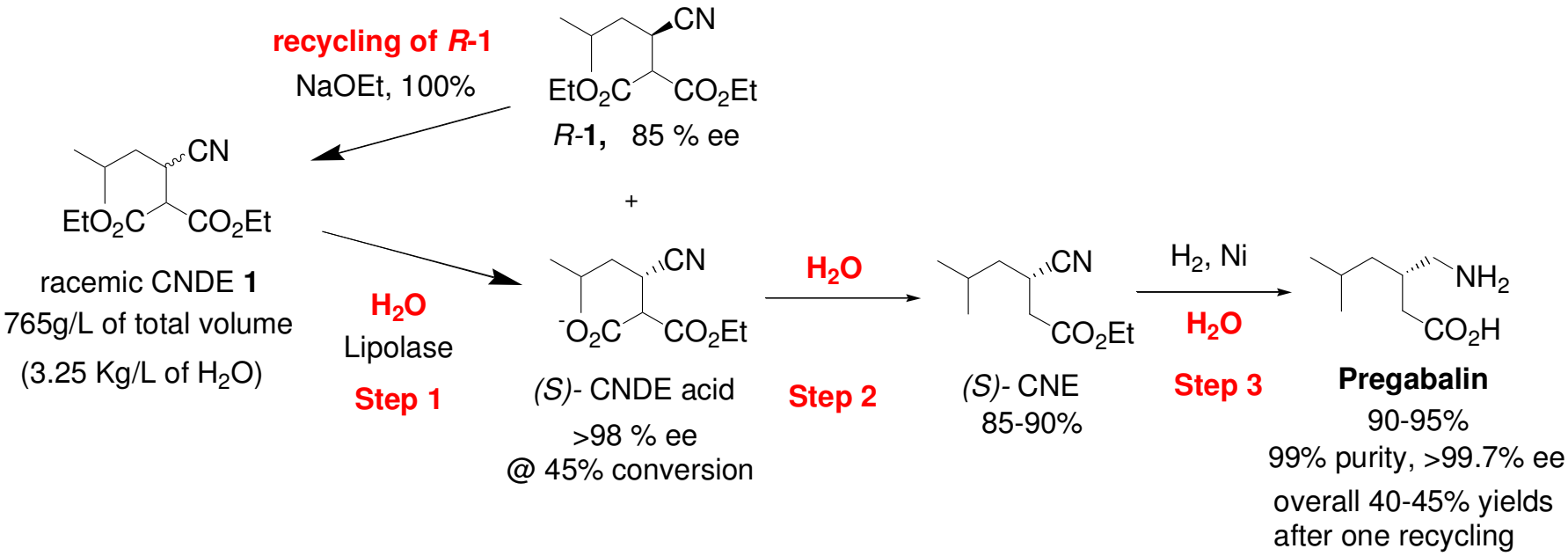


The % value shown is the improvement (reduction in environmental impacts) compared to the worst route selected.

Routes Evaluated (Graph Name)	MW	Comments
QCA-chemical (QCAch)	174	chemical route from Green Chemistry slides
QCA - biocatalytic route (QCA-b)	174	QCA, biocatalytic route from GC slides

Source: Private communication from D. Constable (GSK)

Biocatalytic Kinetic Resolution Route to Pregabalin



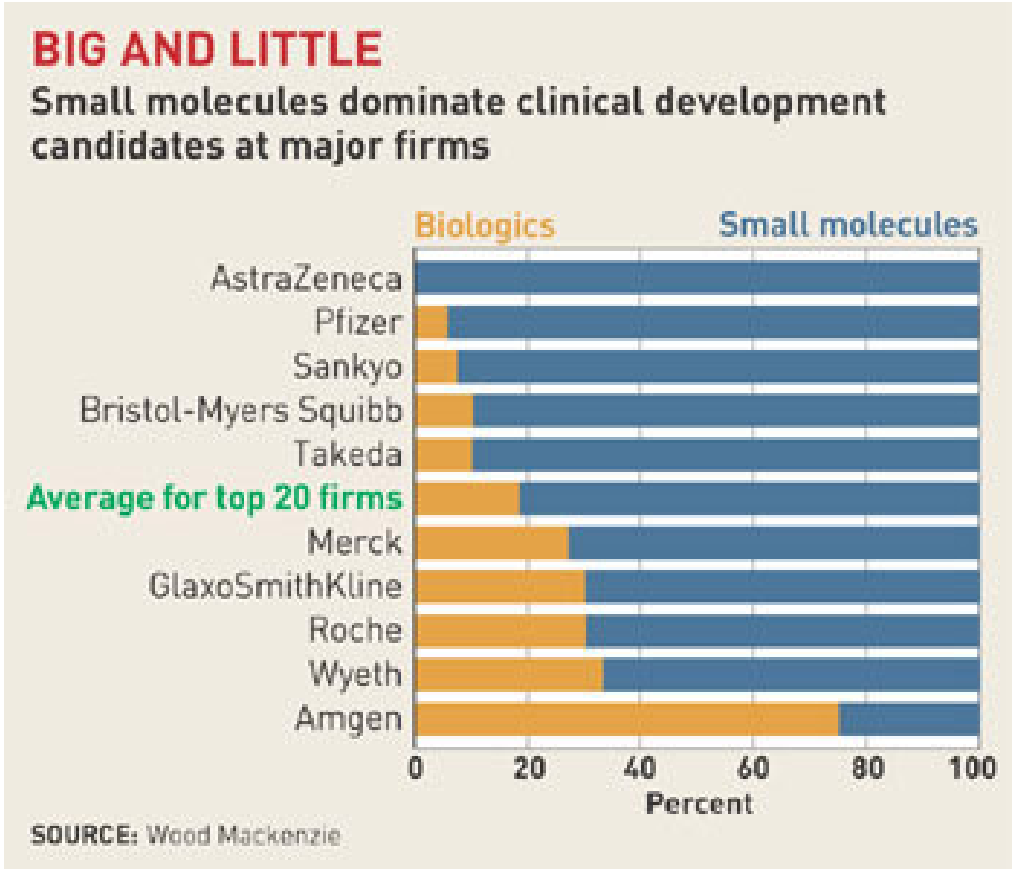
- Biocatalytic with low (~0.8%) protein loading
- Resolution at first step (wrong enantiomer can be recycled)
- High throughput; simple operations
- **All 3 steps conducted in water**

Source: Kim Albizati, Bioverdant (www.bioverdant.com)

Pregabalin Synthetic Improvements

- By replacing all reaction solvents with water, bringing the Resolution to the beginning, and the Raney nickel reduction to the end, the proposed improvements would yield:
  - Starting material usage reduction of 800 tons
  - Solvent reductions:
    - Methanol 400 tons
    - Ethanol 60 tons
    - Tetrahydrofuran 600 tons
    - Isopropanol 2000 tons
  - Mandelic Acid usage eliminated – 1600 tons
  - E-factor = 15!

Pharmaceutical Industry Portfolio Snapshot



Source: C&E News 2005

Biotech Surges in 2005

BIOPHARMACEUTICAL COMPANIES

Amgen and Genentech continue to drive momentum for the biopharmaceutical industry

	FOURTH-QUARTER 2005						FULL-YEAR 2005					
	REVENUES[a] ($ MILLIONS)	EARNINGS[b] ($ MILLIONS)	CHANGE FROM 2004 REVENUES	CHANGE FROM 2004 EARNINGS	PROFIT MARGIN[c] 2005	PROFIT MARGIN[c] 2004	REVENUES[a] ($ MILLIONS)	EARNINGS[b] ($ MILLIONS)	CHANGE FROM 2004 REVENUES	CHANGE FROM 2004 EARNINGS	PROFIT MARGIN[c] 2005	PROFIT MARGIN[c] 2004
Amgen	$3,271.0	$928.0	12.4%	23.9%	28.4%	25.7%	$12,430.0	$4,023.0	17.8%	27.8%	32.4%	29.8%
Amylin Pharmaceuticals	63.5	–67.2	863.2	nm	def	def	140.5	–206.8	309.9	nm	def	def
ArQule	12.3	–2.7	–12.5	nm	def	def	52.9	–7.5	–2.8	nm	def	def
Biogen Idec	632.9	164.6	7.7	61.8	26.0	17.3	2,422.5	541.7	9.5	8.8	22.4	22.5
Celera Genomics	2.1	–17.3	–74.4	nm	def	def	15.3	–53.8	–56.8	nm	def	def
Celgene	149.3	8.0	41.7	–54.1	5.3	16.5	536.9	68.1	42.2	14.3	12.7	15.8
Cephalon	336.4	42.7	12.5	–16.5	12.7	17.1	1,211.9	167.1	19.3	11.9	13.8	14.7
Chiron	615.6	163.8	41.7	nm	26.6	def	1,921.0	259.0	11.5	70.4	13.5	8.8
Genentech	1,893.1	363.3	43.9	61.2	19.2	17.1	6,633.4	1,387.3	43.5	55.1	20.9	19.4
Gilead Sciences	609.3	256.5	64.9	123.5	42.1	31.1	2,028.4	788.8	53.1	78.7	38.9	33.3
Icos	18.8	5.6	–8.0	nm	29.9	def	71.4	–75.8	–4.3	nm	def	def
ImClone Systems	98.2	13.1	–8.5	nm	13.3	def	382.9	98.9	–1.5	–13.0	25.8	29.2
InterMune	28.7	–18.1	–8.3	nm	def	def	110.2	–87.0	–14.4	nm	def	def
Isis Pharmaceuticals	14.6	–7.9	28.6	nm	def	def	40.1	–72.4	–5.9	nm	def	def
MedImmune	492.0	21.4	5.6	–61.0	4.3	11.8	1,243.9	31.4	9.0	–61.7	2.5	7.2
Millennium Pharmaceuticals	122.3	–43.9	21.9	nm	def	def	558.3	–198.2	24.6	nm	def	def
Nabi Biopharmaceuticals	25.3	–75.6	–39.2	nm	def	def	108.1	–128.4	–39.9	nm	def	def
Neurocrine Biosciences	14.1	–23.9	–23.7	nm	def	def	123.9	–22.2	45.5	nm	def	def
Novo Nordisk	1,501.0	190.4	18.7	–18.2	12.7	18.4	5,376.0	934.0	16.3	17.0	17.4	17.3
PDL Biopharma	83.7	7.5	266.4	nm	9.0	def	276.9	16.2	188.4	nm	5.8	def
QLT	50.4	11.7	–6.4	2.6	23.2	21.2	242.0	62.5	30.0	32.7	25.8	25.3
Sepracor	311.1	37.2	136.8	nm	11.9	def	820.9	5.0	115.5	–97.8	0.6	59.3
Serono	669.9	158.7	–1.4	85.5	23.7	12.6	2,586.4	566.2	5.2	28.1	21.9	18.0
Shire Pharmaceuticals	465.0	97.4	24.4	2.3	20.9	25.5	1,599.3	339.6	17.3	–5.0	21.2	26.2
Vertex Pharmaceuticals	63.8	–19.8	60.1	nm	def	def	160.9	–147.1	56.6	nm	def	def
TOTAL[d]	**$11,544.3**	**$2,193.6**	**22.7%**	**64.8%**	**19.0%**	**14.1%**	**$41,093.9**	**$8,289.5**	**22.1%**	**32.2%**	**20.2%**	**18.6%**

a Revenues include product sales, collaborative or contract R&D funding, and royalties. **b** After-tax earnings from continuing operations, excluding significant extraordinary and nonrecurring items. **c** After-tax earnings as a percentage of sales. **d** Percentages calculated from combined revenues and earnings. **def**=deficit. **nm**=not meaningful.

Source: C&E News 2006

Biologicals Are Big Sellers and a Growing Part of the Pharma Portfolio

- Epogen Amgen
  - $3 Billion
- Procrit Johnson & Johnson
  - $3 Billion
- Aramasep Amgen
  - $2.8 Billion
- Enbrel Amgen-Wyeth
  - $2.7 Billion for treating rheumatoid arthritis(+36%)
- Neulasta Amgen
  - $2.2 Billion for treating chemotherapy side effects (+30%)
- Remicade Johnson & Johnson
  - $2.2 Billion (+12%)
- Rituxin (rituximab) Genentech/Biogen-Idec
  - $1.83 Billion in 2005 for treating lymphoma
  - Rheumatoid arthritis could add another $0.5 b

Source: Fortune Magazine 2006

BioPharma Market Cap (March 11, 2007)

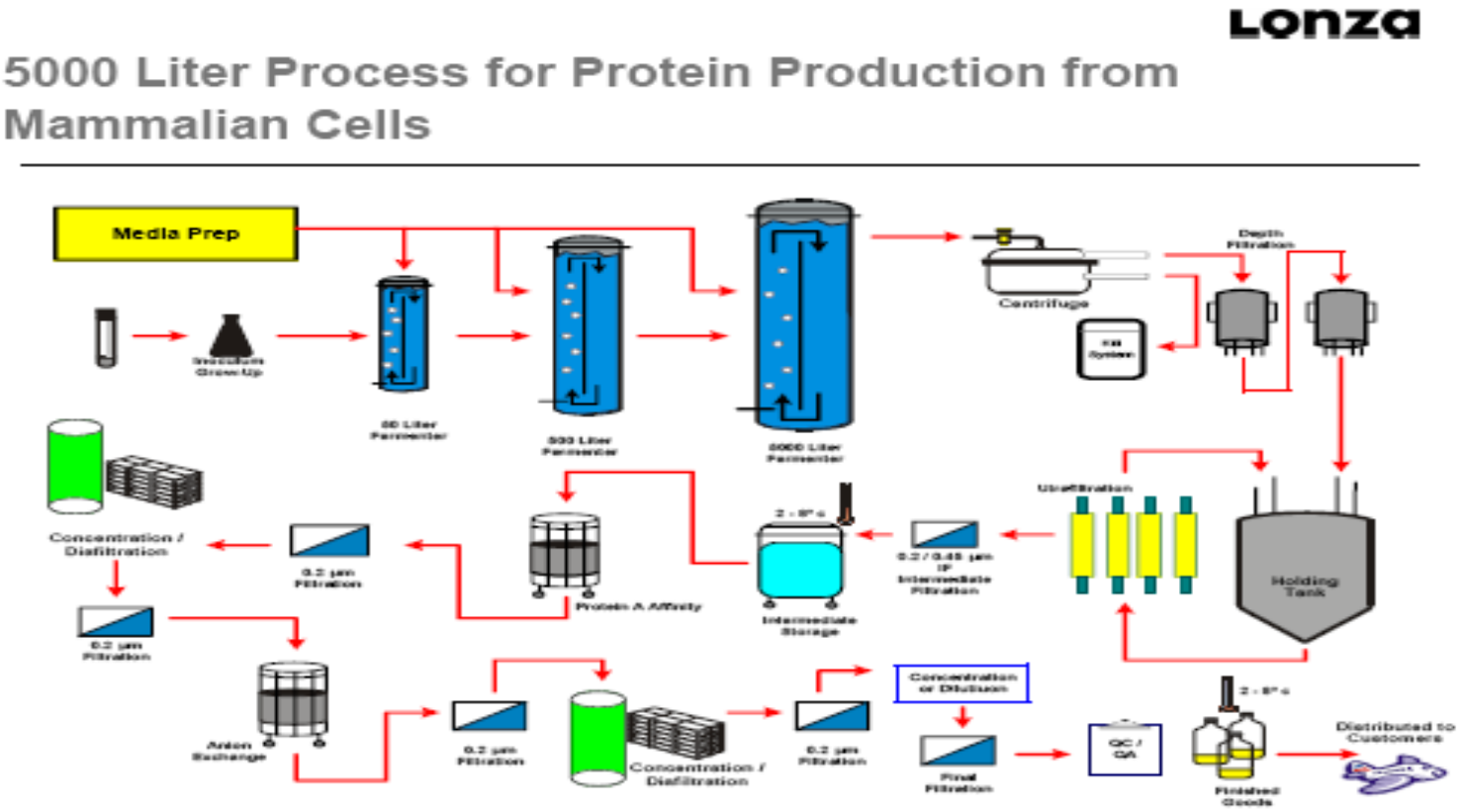
- Amgen (AMGN) $69.1 B
- Biogen-Idec (BIIB) $14.8 B
- Celgene Corporation (CELG) $18.9 B
- Cephalon (CEPH) $4.4 B
- Chiron (CHIR) $9.49 B
- Genentech (DNA) $85.8 B
- Genzyme (GENZ) $15.8 B
- Gilead Sciences (GILD) $32.5 B
- Medimmune (MEDI) $7.5 B
- Millenium (MLNM) $3.4 B
- Novo Nordisk (NVO) $24.2 B
- Sepracor (SEPR) $5.5 B
- MerckSerono SA (SRA) $9.8 B

- Reference Big Pharma: Pfizer (PFE) $179.4B; Johnson & Johnson (JNJ) $179.1 B; Novartis (NVS) $153.6B and GlaxoSmithKline (GSK) $160.7

How Green Are Biological Drugs?

Most answer, “they are green because they are not made by chemical synthesis using organic solvents.”

Monoclonal Antibody Process

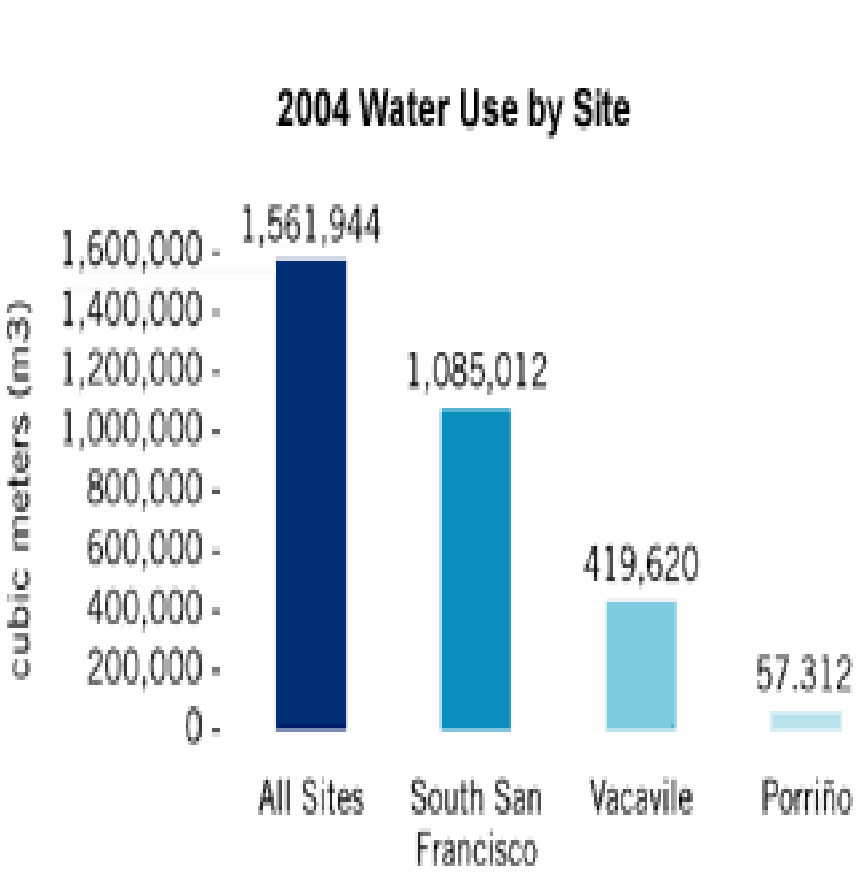


Source:http://www.lonza.com/group/en/company/news/tradefairs/biologics 2004_presentations posters.-ParSys-0039-DownloadFile.tmp/102505%20Future%20Perspectives%20of%20Antibody%20Manufacturing_JB.pdf

Green Chemistry Opportunities with Biological Drug Manufacturing: Relation to Principles

- Water use reduction
  - Principles 1 & 5
- Energy use reduction
  - Principle 6
- Biosafety
  - Principles 5, 10 & 12
- Process Analytical Technology
  - Principle 11
- Solid waste reduction
  - Principles 1 & 4
- Pharmaceuticals in the Environment
  - Principle 10

Genentech Waste Minimization



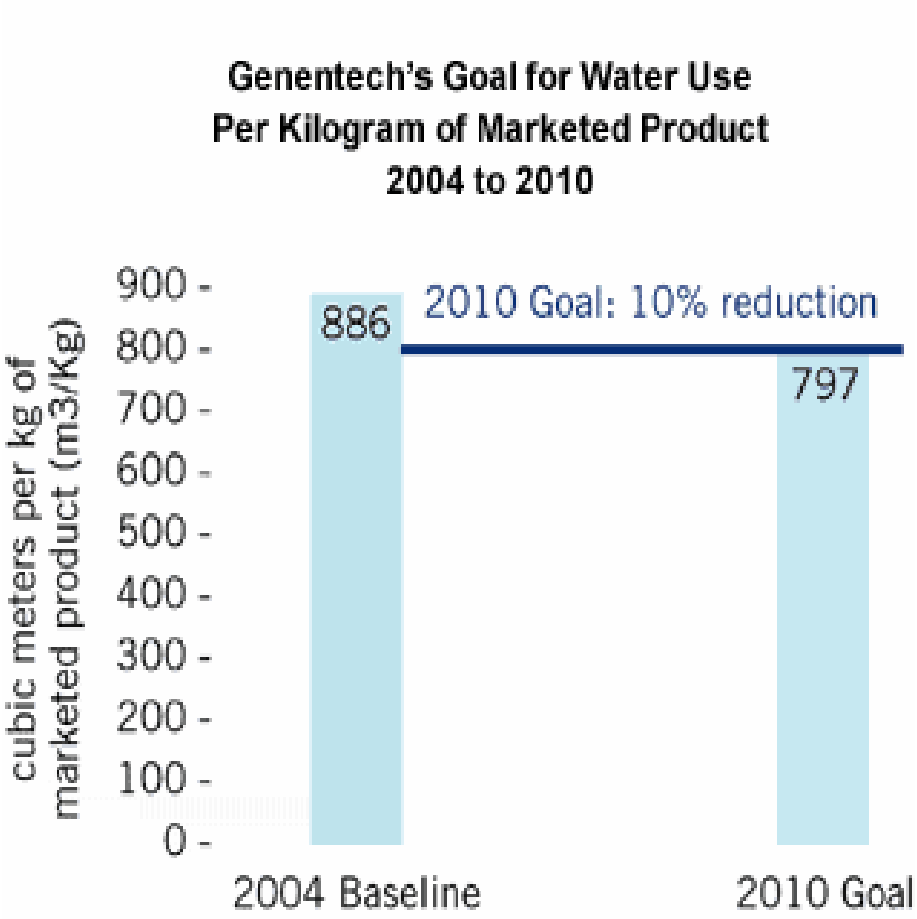
- Water Goal *Improve water efficiency* by 10% by the year 2010, compared to 2004.*

* Water efficiency is measured as total water use divided by kilograms of marketed product produced.

- How Will Genentech Meet This Goal?
  - Reducing the percentage of water that is rejected during the reverse osmosis (RO) purification process
  - Recycling the RO reject water
  - Improving water efficiency on the manufacturing floor

Source: http://www.gene.com/gene/about/environmental/commitment/water.jsp

Genentech's Water Efficiency Goal

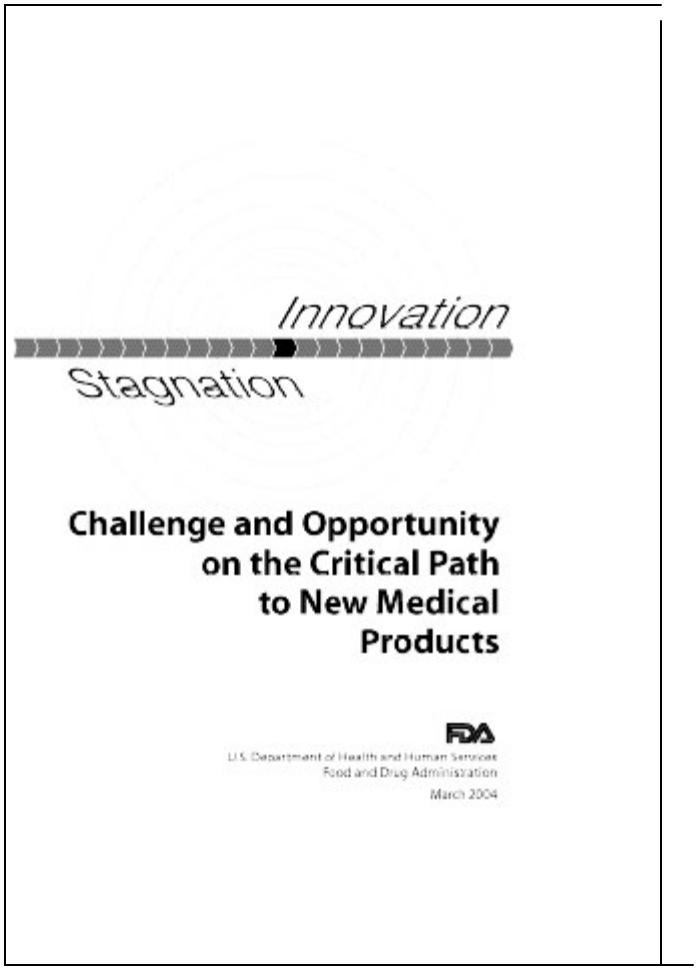


- Water Goal *Improve water efficiency* by 10% by the year 2010, compared to 2004.*

  * Water efficiency is measured as total water use divided by kilograms of marketed product produced

Source: http://www.gene.com/gene/about/environmental/commitment/water.jsp

Bioprocess Mass Spectrometry: A PAT Application, J.S. Alford, *Journal of Process Analytical Technology*, **3**(3),6 (2006)



- FDA report takes pharmaceutical industry to task for lack of innovation
- FDA – Pharma collaborate on right first time/quality by design (QbD) concepts with PAT as a focus
- Green chemistry or benign by design (BbD) intersects with QbD-both lead to better understood and more robust processes
- Green Chemistry principle 11 reads PAT for pharma

Source: www.fda.gov

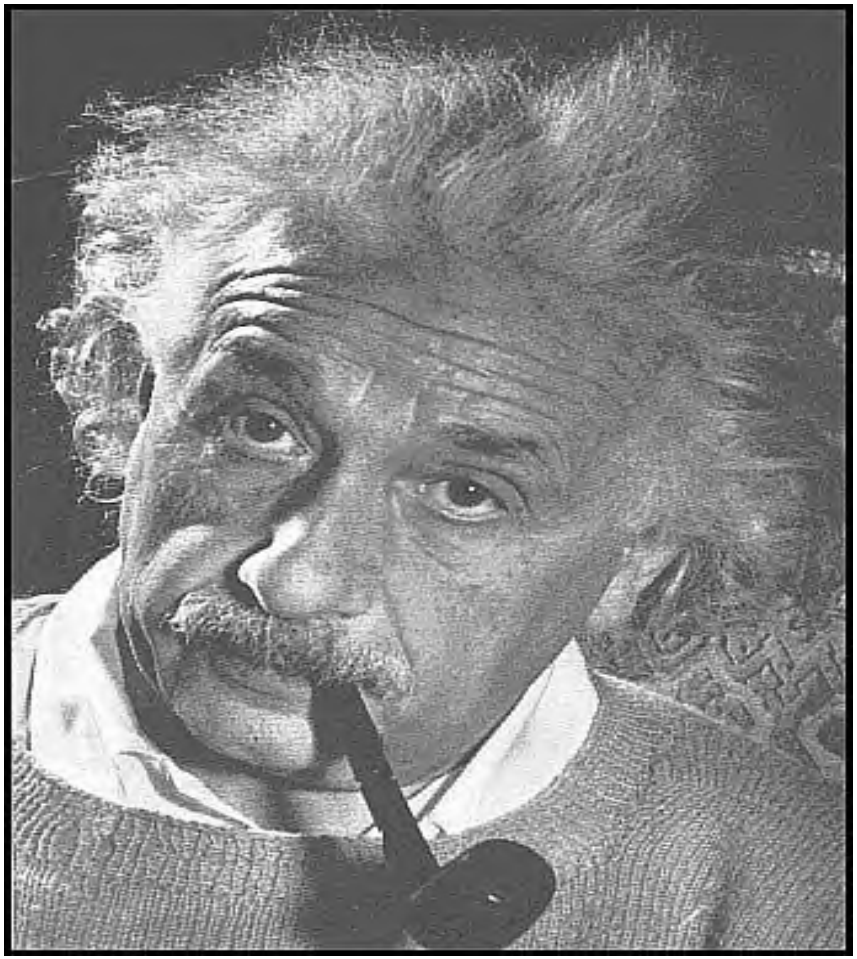
- The 11th Annual Green Chemistry & Engineering Conference will be held at the Capital Hilton in Washington , DC from **June 26-29, 2007**.
- The Call for Papers closed **February 28**.
- Visit http://www.GCandE.org for more details

A Talk Worth Hearing
Sa V. Ho, et. al., 11th Green Chemistry and Engineering Conference

- **Green Technology Assessment Of Therapeutic Protein Manufacture**
- Sa V. Ho, Joseph K. McLaughlin, Andrew C. Espenschied, James F. Bouressa
- Global Biologics, Pfizer Global R&D
- Abstract (in part) Compared to the production of small drug molecules and chemical/petrochemical compounds, the manufacture of therapeutic proteins using biological systems are basically “green”, involving mostly water with little organic solvents or harzardous chemicals, if any. An important environmental index used in the small molecules area is the E-factor, defined as the ratio of the total amount (in kg) of materials used including water to produce 1 kg of the final bulk material. Conceptually green, biologics manufacturing nevertheless consumes very large quantities of water due to a combination of very dilute product synthesis (< 1 wt%) and extensive water usage from complex downstream processing and substantial equipment cleaning. The E factors based on water usage for biologics are thus typically orders of magnitude higher than those for small molecules.

Summary

- Green Chemistry and Engineering are important “hows” in the “how to become sustainable”
- When the claim that small molecule drugs were “green” because their volumes were small compared to products in other chemical industry sectors was examined with a green chemistry lens, a new innovation platform was discovered leading to more efficient, more benign, and more cost effective API processes.
- Now the claim that biological molecules (vaccines, proteins, MAbs) are green by design is starting to be questioned, with preliminary findings that these products have large environmental footprints which should reduce when Green Chemistry and Engineering concepts are applied to their process design.
- The American Chemical Society Green Chemistry Institute Pharmaceutical Roundtable is an effective forum for catalyzing this discussion and implementing these changes. See www.greenchemistryinstitute.org



“The significant problems we face today cannot be solved at the same level of thinking we were at when we created them”

- Albert Einstein